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<p>(21) International Application Number: PCT/GB94/00181</p> <p>(22) International Filing Date: 31 January 1994 (31.01.94)</p> <p>(36) Priority Data:</p> <table> <tr> <td>9302070.9</td> <td>3 February 1993 (03.02.93)</td> <td>GB</td> </tr> <tr> <td>9320187.9</td> <td>30 September 1993 (30.09.93)</td> <td>GB</td> </tr> <tr> <td>9325374.8</td> <td>10 December 1993 (10.12.93)</td> <td>GB</td> </tr> </table> <p>(71)(72) Applicant and Inventor: JENNINGS, Steven, Andrew (GB/GB); 55 East Gox, North Newbold, York Y04 3SD (GB).</p> <p>(74) Agent: BELCHER, Simon, James; R.J. Oulton &amp; Co, c/o Uniquan-Dykes &amp; Lord, Tower House, Medina Way, Leeds LS2 8PA (GB).</p>		9302070.9	3 February 1993 (03.02.93)	GB	9320187.9	30 September 1993 (30.09.93)	GB	9325374.8	10 December 1993 (10.12.93)	GB	<p>(81) Designated States: AT, AU, BE, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SR, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GR, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>	
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9325374.8	10 December 1993 (10.12.93)	GB										
<p>(54) Title: BLENDS OF GLYCINE DERIVATIVES AND SUGARS</p> <p>(57) Abstract</p> <p>A composition which comprises (a) glycine derivative: <math>X^1N = C(NX^2Y) - NX^3 - COX^4X^5 - CO_2H</math> where any one or more of <math>X^1</math>, <math>X^2</math>, <math>X^3</math>, <math>X^4</math> and <math>X^5</math> is hydrogen or lower alkyl, and Y is hydrogen, lower alkyl, or <math>H_2PO_4</math> or a substituted variant thereof, or a salt of the derivative, and (b) a sugar in an amount of from about 2 % to about 98 % by weight of the derivative. Preferably, <math>X^3</math> is methyl, Y is <math>H_2PO_4</math>, and the sugar is a maltodextrin. The sugar is preferably present in an amount of from 40 to 60 % by weight of the glycine derivative.</p>												

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### BLEND OF GLYCINE DERIVATIVES AND SUGARS

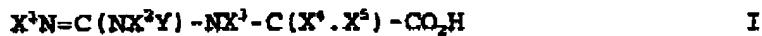
This invention relates to compositions which comprise glycine derivatives and sugars, to pharmaceutical compositions which comprise those compositions and methods of making the compositions.

Creatine exists in muscular tissue of many vertebrates and can be isolated from meat extracts. It has the formula



According to the present invention, it has been found that creatine derivatives blended with one or more sugars can enhance tissue formation in animals.

In one aspect, the invention provides a composition which comprises (a) glycine derivative I



where any one or more of  $\text{X}^1$ ,  $\text{X}^2$ ,  $\text{X}^3$ ,  $\text{X}^4$  and  $\text{X}^5$  is hydrogen or lower alkyl, and  $\text{Y}$  is hydrogen, lower alkyl, or  $\text{H}_2\text{PO}_4$ , or a substituted variant thereof, or a salt of the derivative I, and (b) a sugar in an amount of from about 2% to about 98% by weight of the derivative I.

Preferably,  $\text{X}^1$  is methyl.

Preferably, one or more of  $\text{X}^1$ ,  $\text{X}^2$ ,  $\text{X}^4$  and  $\text{X}^5$  is hydrogen.

Preferably,  $\text{Y}$  is hydrogen, or  $\text{H}_2\text{PO}_4$ , as will result from a reaction of a glycine derivative with phosphoric acid.

Suitable lower alkyl groups which can be used as substituents in the glycine derivative I are  $\text{C}_1$  to  $\text{C}_4$ , straight or branched, groups.

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The glycine derivative I may be present in a hydrated form, for example as the monohydrate.

The glycine derivative may be present as a salt, for example as the sodium or potassium salt.

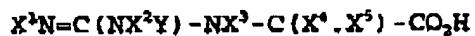
The sugar may be selected from a group consisting of dextrose fructose, glucose and maltose. It is preferred that the sugar is a maltodextrin. Maltodextrins comprise polymers of glucose, and will generally have a dextrose equivalent which is less than about 20, as determined by the Lane-Eynon titration technique (see Pearson's Chemical Analysis of Foods). Maltodextrins can be derived from corn or maize. They often include small amounts of potassium, sodium, and sulphur dioxide.

Preferably, the amount of sugar present in the composition is at least about 30%, more preferably at least about 40%, by weight of the glycine derivative.

Preferably, the amount of sugar present in the composition is not more than about 70%, more preferably not more than about 60%, by weight of the glycine derivative.

In another aspect, the invention provides a pharmaceutical composition which comprises a composition of the type referred to above, in association with a solid or liquid a pharmaceutical carrier or diluent.

In a further aspect, the invention provides a method of making a pharmaceutical composition which comprises mixing (a) glycine derivative I



where any one or more of  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$  and  $X^5$  is hydrogen or lower alkyl, and Y is hydrogen, lower alkyl, or  $H_2PO_4$ , or a

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substituted variant thereof, or a salt of the derivative I, and (b) a sugar in an amount of from about 2% to about 98% by weight of the derivative I.

The composition of the present invention can be used as a metabolic supplement. It can be used to enhance tissue formation, for example in the treatment of diseases, especially wasting diseases such as multiple sclerosis. It has been found that the composition is particularly well suited to enhancing cardiac tissue formation. It can also be used to prevent disease. It has the advantage that its principal constituents occur naturally. Furthermore, the composition has a pleasant taste, and is stable under normal conditions.

The composition has been found to be suitable for use in the treatment of:

- mood disorders, such as bipolar, depressive disorders; recurrent depression disorders; schizo-affective disorders; dysthymia;
- schizophrenia
- dementias, such as Alzheimer's disease; neurotic illness including phobic anxiety disorders; obsessive compulsive disorders; reaction to severe stress; neurasthenia, general anxiety states;
- chronic fatigue syndrome, including myalgia encephalomyelitis (ME).

In another aspect, the invention provides the use of a composition of the type discussed above in the manufacture of a medicament, especially for the treatment of one or more of the conditions referred to above.

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The composition of the invention can be administered in tablet form. It can be administered in powder form. It can be preferred for the composition to be administered in solution, in particular in aqueous solution; it can be particularly preferred to administer the composition in solution, possibly at elevated temperature, which might be the highest temperature at which the solution can comfortably be consumed. For example, the solution might be heated to a temperature which is greater than about 40°C, preferably greater than about 50°C, for example greater than about 60°C, or even higher. Administering the composition in this way has been found to facilitate absorption.

It can be preferred for the temperature of solution to be less than about 55°C when administered, more preferably less than about 45°C, even less than 40°C. This feature allows breakdown of the glycine derivative to be minimised. When the composition is dissolved in solution at a temperature which is elevated to facilitate dissolution, the temperature is preferably then lowered by addition of a liquid at lower temperature (which might be flavoured) to reduce the overall temperature of the solution.

When administered in solution, it can be preferred for the effective concentration of the glycine derivative to be greater than about 0.5% by weight, more preferably greater than about 0.7%, especially greater than about 1.0%. The concentration can be less than about 15% by weight, preferably less than about 10%, more preferably less than about 5%. Suitable concentrations are from about 1.5% to about 5%.

The invention will now be described with reference to certain examples.

#### EXAMPLE 1

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Tablets were formed from a mixture of creatine monohydrate supplied by Chemielinz A G, and a maltodextrin supplied by Roquette Frères S A under the trade name Glucidex 19, in a ratio by weight 2:1, the two constituents being provided in powder form. Tablets were formed using conventional tablet presses from the resulting mixture.

**EXAMPLE 2**

Tablets were formed from a mixture of the creatine monohydrate used in Example 1 and a glucose polymer supplied by Edward Mendell & Co under the trade name Endex, in a ratio by weight 2:1, the two constituents being provided in powder form. Tablets were formed using conventional tablet presses from the resulting mixture.

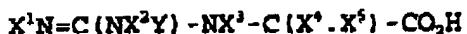
**EXAMPLE 3**

Tablets were formed from a mixture of the creatine monohydrate used in Example 1 and a dextrose polymer supplied by Cerestar Limited under the trade name Cellellose, in a ratio by weight 2:1, the two constituents being provided in powder form. The mixture of the powders was supplied for ingestion in powder form.

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CLAIMS:

1. A composition which comprises (a) glycine derivative I



I

where any one or more of  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$  and  $X^5$  is hydrogen or lower alkyl, and Y is hydrogen, lower alkyl, or  $H_2PO_4$ , or a substituted variant thereof, or a salt of the derivative I, and (b) a sugar in an amount of from about 2% to about 98% by weight of the derivative I.

2. A composition as claimed in claim 1, in which  $X^3$  is methyl.

3. A composition as claimed in claim 1 or claim 2, in which Y is  $H_2PO_4$ .

4. A composition as claimed in any one of claims 1 to 3, in which the sugar is selected from a group consisting of dextrose, fructose, glucose and maltose.

5. A composition as claimed in claim 4, in which the sugar is a malcodextrin.

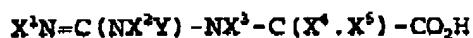
6. A composition as claimed in any one of claims 1 to 5, in which the sugar is present in an amount of from about 30% to about 70% by weight of the glycine derivative.

7. A composition as claimed in claim 6, in which the sugar is present in an amount of from about 40% to about 60% by weight of the glycine derivative.

8. A pharmaceutical composition which comprises a composition as claimed in any one of claims 1 to 7 in association with a solid or liquid carrier or diluent.

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9. A method of making a pharmaceutical composition which comprises mixing (a) glycine derivative I



I

where any one or more of  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$  and  $X^5$  is hydrogen or lower alkyl, and Y is hydrogen, lower alkyl, or  $H_2PO$ , or a substituted variant thereof, or a salt of the derivative I, and (b) a sugar in an amount of from about 2% to about 98% by weight of the derivative I.

10. A method as claimed in claim 9, in which the glycine derivative I and the sugar are mixed in powder form.

11. Use of a composition as claimed in any one of claims 1 to 7 in the manufacture of a medicament.

## INTERNATIONAL SEARCH REPORT

Internat. Application No.  
PCT/GB 94/00181A. CLASSIFICATION OF SUBJECT MATTER  
IPC 5 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Class or document, with indication, where appropriate, of the relevant passage	Relevant to claim No.
X	EP,A,B 339 814 (UNITIKA LTD) 2 November 1989	1-4,6-9
Y	see page 4, line 39 - page 5, line 2	5
X	EP,A,B 370 994 (LUBEC, GERT, PROF. DR.) 30 May 1990	1,2,4,8, 9,11
Y	see column 7, line 20 - line 52	5
X	GB,A,1 208 398 (CALBIOCHEM) 14 October 1970 see examples 1-3	1-4,8-10

 Further documents are listed in the continuation of box C. Patent family members are listed in box A.

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1 Date of the actual completion of the international search

Date of mailing of the international search report

2 May 1994

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Information on parent family members

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